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Are Linoleic Acid Supplements Beneficial in Increasing Growth in Pediatric Cystic Fibrosis Patients?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective:
The objective of this selective EBM review is to determine "Are linoleic acid supplements beneficial in increasing growth in pediatric cystic fibrosis patients?"

Study Design:
Review of three English primary studies published between 1995 and 2000.

Data Sources:
Two randomized control trial and one controlled clinical trial were used.
Studies were found using PubMed and Cochrane Databases.

Outcomes Measured:
Primary outcomes measured include the taste, smell, and appearance of the supplement and the growth of the cystic fibrosis patients.

Results:
In Steinkamp G, Demmelmair et al., the treatment group grew in its weight-for-height; whereas, there was no change in the growth/ body weight of the control group. Furthermore, the treatment group had an overall weight gain of 1.2 kg. In van Egmond et al., the participants using the supplement with more linoleic acid grew better than those using a supplement with less linoleic acid. In Rettammel AL, Marcus MS et al, fifteen of the twenty-four participants used an oral supplement before and ten of those individuals preferred this supplement. The supplement was well tolerated with fourteen participants preferring the taste of the supplement; however, seven participants thought the supplement was inconvenient and reported that the supplement was difficult to reconstitute.

Conclusions:
The results of the two randomized control trials and a controlled clinical trial demonstrated that linoleic acid supplements increase growth in pediatric cystic fibrosis individuals. Future study is warranted to evaluate the proper amount of linoleic acid needed to increase growth, and different techniques need to be carried out in order to improve the taste and convenience of the supplement. The trials were not double blind studies and had a small sample size, which may have limited the data formulated.

Keywords:
Linoleic acid supplements, cystic fibrosis, pediatrics, malnutrition.

Introduction

Cystic Fibrosis (CF) is an inherited, life-threatening disease that causes the body to produce high levels of mucus, primarily affecting the lungs and pancreas.[1] In addition to hindering an individual's breathing, the mucus obstructs the pancreas and decreases the release of pancreatic enzymes which stops the body from breaking down and absorbing food.[2] Various symptomatic treatments have aided patients in their ability to breathe easier and to thin copious amounts of their mucous production; however, considerations of the metabolic disturbances are vital in their management as well. One such supplement, linoleic acid, can be beneficial and effective in the growth of pediatric cystic fibrosis patients.

The incidence of CF is approximately 1,000 new cases each year affecting 30,000 people in the United States and 70,000 people globally. The ratio of an individual being a carrier of this disease to a non-carrier is 1:31 American families.[2] The treatment for CF is approximately $50,000- $74,000 per year.[3] The number of healthcare visits each year is unknown because it varies based on the severity of a patient's disease. There are multiple routine visits each year, but some patients may need to be hospitalized based on their exacerbations and lung function.[2]

The CF gene "makes a protein called the CF Transmembrane conductance Regulator (CFTR), which is a chloride channel."[4] This channel allows Chloride followed by water to flow out of the cells and keeps the mucus thin as it travels out of the lungs. CF is caused by a defective gene of the CFTR, which produces copious, adhesive-like mucus secreted over the lungs, pancreas and reproductive system. Due to the increased mucus secretion over the lungs, CF individuals will attract bacteria and have numerous lung infections. Furthermore, the thick secretions can obstruct the pancreas and prevent necessary enzymes from being produced during digestion leading to poor growth and reduced nutrition.[2] Common symptoms include salty skin,

cough, unctuous stools, wheeziness and shortness of breath. Even though the cause of CF is known, there is not a definite cure. The CF foundation has made strides in its funding and researching in order to prolong the quality and quantity of life.

The usual methods to treat CF are symptomatic. The mainstay treatments are airway clearing (postural drainage/ percussion, or inflatable vests) and nutrition supplements, such as a high calorie diet, pancreatic enzyme replacements, and vitamin D. Additional treatment regimens consist of inhaled medications, bronchodilators, mucolytics, hypertonic saline, and antibiotics, such as Azithromycin, Tobramycin, or Ciprofloxacin. Depending on the severity of the illness, an individual may need nasal polyp removals, a lung transplant, oxygen therapy, or a feeding tube.[2] New treatments are currently in trials that are meant to treat the underlying cause of CF. Since the risk of malnutrition is high in individuals with CF, Linoleic acid supplements may be used to aid in the growth of CF individuals. Those with malnutrition have a deficiency in essential fatty acids which can decrease their overall health leading to poorer outcomes. Energy rich supplements containing linoleic acid may be beneficial in the treatment regimen of those with CF. This selective evidence-based medicine review evaluated two randomized control trials and one controlled clinical trial to examine the growth of pediatric cystic fibrosis individuals taking linoleic acid supplements.

Objective

The objective of this selective EBM review is to determine "Are linoleic acid supplements are beneficial in increasing growth in pediatric cystic fibrosis patients?"

Methods

The criteria used for the selection of studies included pediatric CF patients with significantly low body weight. The intervention studied in one randomized control trial consisted of an oral

energy supplement containing linoleic acid with dietary counseling; whereas the other randomized control trial used predigested formula containing 12% of total energy of linoleic acid. The controlled clinical trial consisted of a powder nutrition supplement with more energy, fat and linoleic acid. The first randomized control trial compared a control group of cystic fibrosis patients receiving dietary counseling only; whereas the second randomized control trial compared predigested formula containing 7% of total energy of linoleic acid. The controlled clinical trial compared the individuals enrolled in this study to their own results before and after the use of the supplement. Measured outcomes that are being utilized are the taste, smell, and appearance of the supplement and the growth of the patients. The study types involved two randomized control trials and one controlled clinical trial.

Key words used to acquire literature included "linoleic acid supplements," "cystic fibrosis," "pediatrics," and "malnutrition." All articles were published in peer reviewed journals and all were in the English language. The articles were all searched by the author through PubMed and Cochrane Databases. They were selected based upon their relevance and importance to patient oriented evidence that matters (POEMS). Inclusion criteria consisted of studies that were randomized controlled and included patient-oriented outcomes. Also, the inclusion criteria consisted of individuals with cystic fibrosis that have a significantly low body weight below 95% of normal for height. Exclusion criteria consisted of those who were older than 18 years of age and articles that addressed disease-oriented evidence (DOE). Statistics were reported based on p-values and standard deviation. Table 1 demonstrates the demographics and characteristics of the included studies.

Table 1 – Demographics and Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Steinkamp (2000)[5]	RCT	36	> 4 years old	Patients with CF that have low body weight	-Patients less than 4 years old -Patients with DM or liver cirrhosis -Received oxygen therapy or nocturnal gastrostomy feeding	0	An oral energy supplement containing linoleic acid with dietary counseling.
Rettammel (1995)[1]	Controlled Clinical Trial	24	>4 years old	Patients with either a decrease in one growth channel in weight for age during the previous year, a plateau in weight gain for 3 months or longer, or an adequate growth dependent on prescribed nutritional supplement	Patients that have not been diagnosed with pancreatic insufficiency	7	A powder nutrition supplement with more energy, fat and linoleic acid that was taken at least once a day depending on the age of the individual.
van Egmond (1996)[6]	RCT	76	Infants followed for 9 yrs	-A patient at University of Wisconsin -Diagnosed by 9 months of age and had dietary records indicating they were fed predigested formula	Infants that had been breast fed	11	Predigested formula containing 12% of total energy of linoleic acid.

Outcomes Measured

Each of the three trials assessed the effect of linoleic acid supplements on the growth of the cystic fibrosis individuals and/or the acceptability and tolerance of the supplement. The growth of the individuals was measured by height and weight. Van Egmond et al. assessed the growth outcome by measuring the individuals' weight-for-age (WAZ) and height-for-age (HAZ). The ANTHRO software was used to calculate the Z scores.[6] Rettammel AL, Marcus MS et al assessed the taste, smell and appearance of the supplement that was measured by a questionnaire. The questionnaire rated the taste, smell, appearance and mouth feel of the supplement on a scale of "poor-fair-good-excellent."[1] Also, the trial measured growth by calculating Z scores using the CASP program.[1]

Results

Two trials evaluated the efficacy of linoleic acid supplements on the growth of individuals with cystic fibrosis. The randomized control trials compared linoleic acid supplements to a supplement reduced in linoleic acid or strictly dietary counseling; whereas the controlled clinical trial compared the growth before and after the intervention.

The randomized control trial (Steinkamp G, Demmelmair et al.) compared the use of an oral supplement containing linoleic acid with an addition of dietary counseling to a control group of cystic fibrosis patients receiving dietary counseling only. This was a three month long trial that included patients with CF that have significantly low weight-for-height below 95%. It excluded patients less than four years old, those with diabetes mellitus, or liver cirrhosis and individuals who received oxygen therapy or nocturnal gastrostomy feeding. There were thirty-six participants and none of the individuals discontinued the trial. The participants' height and weight were measured before the intervention and after the three month trial. The dietary

counseling was given to all participants at the baseline visit. Sixteen patients were randomly chosen to enter the treatment group; whereas twenty were chosen for the comparison group. In order to compare baseline and post treatment values, paired t-tests were completed, and grouped t-tests were carried out for the comparison groups.[5] Finally, the results were shown to be statistically significant with a p value < 0.05. The treatment group grew in its weight-for-height; whereas, there was no change in the growth/ body weight of the control group. Furthermore, the treatment group had an overall weight gain of 1.2 kg.

Table 2: Treatment vs. Control Group[5]

	Supplemented group (N=16)		**Comparison group (N=20)**		**p-value**
	Before	*After*	*Before*	*After*	< 0.05
Length (cm)	147 ± 15	148 ±16	135 ± 22	136 ± 21	
Weight (kg)	32.2 ± 8.9	33.4 ± 9.6	27.3 ± 7.6	27.5 ± 7.5	
Weight-for-height (% of predicted)	82.8 ± 8.6	84.8 ± 9.6	87.8 ± 8.7	85.6 ± 10	
Body fat (kg)	5.1 ± 1.7	5.8 ± 2.2	4.4 ± 1.6	4.3 ± 1.4	

The other randomized control trial (van Egmond et al.) compared the use of predigested formula containing 12% of total energy linoleic acid (formula A) to predigested formula containing 7% of total energy of linoleic acid (formula B). This was a longitudinal study that lasted for nine years. In order to be included in the study, the participants had to be patients at the University in Madison or the Children's Hospital of Wisconsin in Milwaukee, diagnosed by 9 months of age and were fed predigested formula. The exclusion criteria consisted of infants that had been breast-fed. There were 76 infants who began the study and 11 participants discontinued. The comparison of the formula containing 12% linoleic acid to 7% of linoleic acid assessed the growth of the participants which were measured by their height and weight at diagnosis and subsequent times defined by the various protocols (i.e. ages 1.5, 3, 4.5, 6, 7.5, 9,

10.5, 12, and 15 months). The height, weight and Z scores were calculated by using the ANTHRO software.[6] Even though forty-three participants were fed formula A and 33 were fed formula B, there were no significant differences between the two groups at baseline. Participants using formula A grew better than participants using formula B and was statistically significant for the height-for-age Z scores with a p value of 0.049. However, the results for the weight-for-age Z scores were not statistically significant with a p value of 0.081.

Table 3: HAZ and WAZ scores at follow-up during infancy[6]

	Height-for-age Z score	**Weight-for-age Z score**
SD	1.18	0.98
Mean	-0.24	-0.74
P value	0.049	0.081

The controlled clinical trial (Rettammel AL, Marcus MS et al.) compared the taste, smell, and appearance of the linoleic acid supplement and growth of CF patients. The intervention consisted of a powder nutrition supplement with more fat, energy and linoleic acid that was taken at least once a day depending the patient's age. Participants ages 5-10 consumed one 8oz serving per day; ages 11-17 consumed two 8oz servings per day and ages 18 and older consumed three 8oz servings per day. This was a three month long trial that included patients older than four years old that were not participating in other research protocols, and either had a decrease in growth in weight-for-age or weight-for-height, had a plateau in weight gain for three months or had an adequate growth dependent on the use of a prescribed nutrition supplement.[1] This trial excluded those who had not been diagnosed with pancreatic insufficiency. There were twenty-four participants in the study and seven discontinued the trial due to noncompliance, a secondary diagnosis of muscular dystrophy, or an intolerability of the supplement because of a cholecystectomy or vomiting. Of the seventeen remaining participants, eleven were pediatric participants under the age of eighteen years old and six were older than eighteen years old. The

growth of the participants was measured by their height and weight at baseline and their final visit after their three month trial. There was no change in weight for the adult participants, but there was a significant gain in weight seen in pediatric children (p value= 0.02). There were "no significant changes in skinfold measurements of z scored for weight and height."[1] However, one pediatric participant had an individual growth improvement with a weight gain of 2.5 kg and a 4.4 cm increase in height.

Furthermore, the participants used a questionnaire in order to discuss the overall taste and acceptability of the supplement. Even though seven subjects discontinued the trial, all twenty-four subjects were included in the questionnaire. Fifteen of the twenty-four participants used an oral supplement before and ten of those individuals preferred this supplement. Overall, the supplement was well tolerated with fourteen participants preferring the taste of the supplement. Four participants reported mild nausea, fullness and bloating. Seven participants thought the supplement was inconvenient and reported that the supplement was difficult to reconstitute. The compliance positively correlated with weight gain (r=0.98) with the mean compliance of 69%.

Table 4: Acceptance and Tolerability of the Supplement[1]

	Taste	**Smell**	**Appearance**	**Mouth feel**
Poor	3	0	0	6
Fair	7	12	11	10
Good	13	11	13	8
Excellent	1	1	0	0

Discussion

This selective EBM review investigated two randomized controlled trials and a controlled clinical trial for the efficacy of increasing growth in cystic fibrosis individuals and the tolerability of the linoleic acid supplement. It is known that individuals with CF can become malnourished and have an overall decrease in growth. Supplementing with linoleic acid, an

omega-6 polyunsaturated fatty acid, was beneficial because the three trials demonstrated that the linoleic acid supplements did increase growth. This data was statistically significant in the RCT by Steinkamp G, Demmelmair et al., and those receiving the supplement grew and benefited from the intervention.[5] In van Egmond et al., infants consuming a formula with a larger content of linoleic acid grew more and had a higher weight gain. Therefore, cystic fibrosis infants require a high intake of linoleic acid in order to achieve optimal growth.[6] In Rettammel AL, Marcus MS et al., this supplement was shown to be tolerated and accepted by most; however, improving the reconstitution of the supplement in puddings, and other baked products may be beneficial for those who considered the supplement to be inconvenient.

There were several limitations among the trials presented in this selective EBM review, and few randomized control trials recently established narrowed the source for reference data. The two randomized control trials were not double blind studies. Limitations in Rettammel AL, Marcus MS et al. include the small sample size, the variability, and the short three month time period. Even though the three month trial period was an adequate time to define tolerability and acceptability of the supplement, it was not a sufficient time to determine growth of the participants.[1] In van Egmond et al., a "time-bias of patient management" was considered a limitation in this trial.[6] For all three trials, the results may have been influenced by these limitations.

Linoleic acid supplements have demonstrated to be advantageous in other disease states as well. For example, linoleic acid supplements can be used in those who are deficient in linoleic acid, adult patients with end-stage liver disease, have hypertension or dermatitis.[7] Additionally, it is beneficial in improving premenstrual syndrome symptoms, multiple sclerosis, and neurodegenerative disorders. Hypersensitivity to linoleic acid or its derivatives is a

contraindication. Some adverse reactions include bloating, metabolic effects, or allergic inflammation.[7] There is no teratogenicity data available, and Orlistat has been found to be a potential drug interaction because it decreases the absorption of linoleic acid.[7]

Cystic fibrosis is a life- threatening disease that does not have a current cure; however, numerous funding and research has been accomplished to expand the quality and quantity of life. For example, Kalydeco was FDA approved in 2012 and is a new medication that treats CF individuals 6 years and older with the CF mutation G551D.[8] It improves lung function and helps the patients gain weight by decreasing the sweat chloride levels.[8] This medication has helped many people with CF with the particular mutation; however, it does not work for other mutations. The CF foundation continues to explore different research topics and new medications in the hope of finding a cure for this disease. Until a cure is possible, maintaining lung function, improving nutrition and preventing infections are the symptomatic mainstay treatment regimens.

Conclusion

It is concluded that the three trials included in this selective EBM review determine that pediatric cystic fibrosis individuals can have an increase in growth with linoleic acid supplements. Even though there were limitations in these trials, the participants did grow. In addition to increasing the sample size and extending the time periods in the trials, future study is warranted to evaluate the proper amount of linoleic acid needed to increase growth. Additional testing and experimentation are required in order to ascertain the appropriate weight of CF individuals at which the linoleic acid supplement would be more beneficial than increasing dietary intake. Furthermore, various recipes or different blending techniques can be discussed in order to improve the taste and convenience of the supplement; however, it can be seen as a

positive addition as an oral nutritional supplement to cystic fibrosis treatment regimens. Even though cystic fibrosis is incurable at this time, continued research and trials will only improve the quality of life of CF individuals and eventually find a cure for this disease.

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